PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant:	Watkins, Jeffry D.	Group Art Unit: 1644
Serial No.:	10/553,938	Examiner: Ron Schwadron, Ph.D.
Application Date:	October 21, 2005	Confirmation No.: 8652
For:	CD20 Binding Molecules	
Docket No.:	X-16760A	

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Derrick R. Witcher, declare that:

1. I hold the degree of Ph.D. in Pharmacology, received in 1991 from the Department of Pharmacology at the Indiana University School of Medicine. My Ph.D. thesis was entitled "Characterization of the multifunctional Ca2+/calmodulin dependent protein kinase phosphorylation of the cardiac ryanodine receptor." I have authored or co-authored over 30 scientific research papers related to biotechnology and recombinant molecular biology.

2. I have been employed since 1997 by Eli Lilly and Company (hereinafter, "Lilly") in Indianapolis, Indiana. Currently, I am a Senior Research Advisor in the Protein Optimization Group for Biotech Discovery Research at Lilly, and I lead various research project teams largely focused on the engineering of therapeutic proteins and monoclonal antibodies for improved therapeutic performance. In this capacity, I have been involved with or contributed to between 6 to 8 therapeutic antibody humanization and/or optimization efforts, some of which involved collaboration with research scientists at Applied Molecular Evolution, Inc., a wholly-owned subsidiary of Lilly.

3. My previous positions at Lilly were:

Research Advisor	2006 - 2010
Principle Research Scientist	2003 – 2006
Senior Scientist	1997 – 2002

4. Additionally, I was employed from 1995 to 1997 at Pioneer Hi-Bred Int'l. Inc. My responsibilities included leading research teams focused on the expression of high value proteins in plants and coordinating the production of human therapeutic proteins in plants.

5. I have read and understand U.S. Patent Application Serial No. 10/553,938 (hereinafter, the Watkins, et al. patent application), and I am familiar with the Final Office Action dated April 1, 2011, in the Watkins, et al. patent application.

6. I understand that the Examiner has cited as prior art against the Watkins, et al. patent application a Business Wire article entitled "Applied Molecular Evolution Advances Optimized Versions of anti-TNF alpha and anti-CD20 Monoclonal Antibody Therapeutic Candidates", dated January 3, 2003 (hereinafter, referred to the "Business Wire" reference).

7. I understand that the invention disclosed in the Watkins, et al. patent application is directed to CD20 binding compositions (e.g., antibodies) comprising a set of three structurally defined heavy chain CDRs and a set of three structurally defined light chain CDRs. The presently claimed invention is based on detailed experiments involving antibody optimization which resulted in functionally improved CD20 binding antibodies comprising the CDRs defined by specific amino acid sequences.

8. I have also read and understand the Business Wire reference cited as anticipating prior art against the subject matter presently claimed in the Watkins, et al. patent application. In relevant part, the Business Wire reference describes, in entirely functional terms, a CD20 binding antibody, AME-133, reported to have improved functional attributes as compared to Rituxan® (i.e., a therapeutic CD20 binding antibody known and commercialized at the time of publication of the Business Wire reference).

9. Antibodies are chemical compounds, and like any chemical compound, an antibody has a specific molecular structure and can be readily characterized by that structure. The function

of antibodies that is relevant for the present discussion is their capability to bind specifically to a different molecule, in this case the B-cell lymphoma expressed protein, CD20, which is referred to as the antibody's target or antigen. Antibodies are comprised of polymer strings of amino acids, referred to as "chains." Each chain of an antibody is conventionally discussed in terms of certain "regions" known as "constant regions" and "variable regions." Variable regions are primarily responsible for antigen binding as well as for the great structural diversity that exists among antibodies. Further, variable regions are comprised of framework regions and complementarity determining regions (CDRs). Framework regions, whose precise structures can vary significantly from one antibody to another, orient the CDRs such that the antibody can bind the antigen. The CDRs, which display even greater variability, directly interact with and bind to the antigen (e.g., CD20).

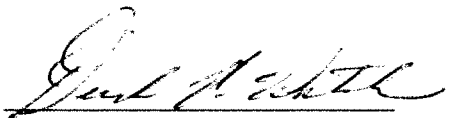
10. It is impossible to predict which of the twenty naturally occurring amino acids exists at each position in the variable region of an antibody based on the structure of the antigen. The entire premise upon which antibody-based medicine rests is dependent on these variable and completely unpredictable chemical structures.

11. Based on my experience and knowledge gained from years of training and working as a research scientist in the relevant art, generally described as recombinant protein engineering and production, I conclude that the Business Wire reference provides essentially no practical or useful guidance to the skilled artisan in the relevant field with respect to making the subject matter claimed in the Watkins, et al. patent application. Therefore, an ordinarily skilled researcher in the relevant field of research at the time just prior to the effective filing date of the Watkins, et al. patent application (i.e., May 20, 2003) would have needed to experiment unduly and demonstrate inventive ability in order to make the invention that is presently claimed even if they had possessed full knowledge of the state of the art (including the Business Wire reference). In other words, significant innovation would have been required of a skilled artisan in order to achieve an antibody with the identical set of CDRs, variable region sequences, or full-length heavy and light chains as the claimed compositions. Furthermore, the art of antibody optimization was at the time, and still remains today, largely an unpredictable art with almost limitless potential for varying the CDRs and/or variable region sequences of antibodies with unknowable and unpredictable consequences to the ability of the resulting compositions to function effectively as CD20 binding compounds.

12. Discovery and development of human-engineered antibodies was at the relevant time (and presently still) a complex endeavour and unpredictable in terms of what sequence would eventually confer the desired antibody properties. It is not possible to predict which amino acid changes in an antibody molecule will confer improved properties upon the parent molecule. It requires a process of constructing and analyzing numerous, and oftentimes hundreds, of antibody mutants. It is not possible to predict how changes in amino acid sequence will affect the folding of the antibody protein or the binding of the antibody to an antigen. Changing even one or two residues may modify the affinity or specificity of an antibody.[1] It is almost always the case that developing an antibody with optimal characteristics requires extensive research and analysis of the exact sequence which will yield the desired effects.

13. In sum, even a skilled researcher in the relevant art with knowledge of the relevant art at the time just prior to the effective filing date of the Watkin's, et al. patent application would not be able to make the compositions presently claimed in the Watkin's et al. patent application without undue experimentation.

14. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and may jeopardize the validity of this application or any patent issuing thereon.



Derrick R. Witcher, Ph.D.

June 1, 2011

Date

[1] Roberts et al., *Nature* 328:731-734 (1987); Winkler et al., *Journal of Immunology* 2000, 165:4505-4514; Schildbach, et al., *Protein Science* 3:737-749 (1994).